

Labeling Attachment:

**Confidential –
Not For Public Disclosure**

**APPEARS THIS WAY
ON ORIGINAL**

WITHHOLD 13 PAGE (S)

DRAFT

Labeling

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Paul Levine
7/26/02 02:01:39 PM
CSO

Joyce Korvick
7/27/02 02:03:42 PM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF TELECON

DATE: JUNE 26, 2002

APPLICATION NUMBER: NDA 21-200, Zelnorm™ (tegaserod) Tablets

BETWEEN:

Novartis Pharmaceuticals Corporation

Martin Lefkowitz, M.D., Executive Director, Clinical Research & Development

David Earnest, M.D., Clinical Research Physician, Clinical Research & Development

Bo Joelsson, M.D., Global Therapeutic Area Head, Gastroenterology

Kurt Graves, Senior Vice-President and General Manager, US Commercial Operations

Mathias Hukkelhoven, Ph.D., U.S. Head of Regulatory Affairs

Phillip Bently, Ph.D., Preclinical Safety

Donna Vivelo, Associate Director, Drug Regulatory Affairs

Phone: (973) 781-3572

AND

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Joyce Korvick, M.D., M.P.H., Deputy Director

Hugo E. Gallo-Torres, M.D., Ph.D., Medical Team Leader, GI Drugs

Jasti Choudary, B.V.Sc., Ph.D., Supervisory Pharmacologist

Ray Frankewich, Ph.D., Chemistry Reviewer

Paul E. Levine, Jr., R.Ph., Regulatory Project manager

Office of Drug Evaluation III (HFD-103)

Florence Houn, M.D., M.P.H., Director

Division of Biometrics II (HFD-715)

Edward Nevius, Ph.D., Division Director

Tom Permutt, Ph.D., Statistical Team Leader

SUBJECT: To discuss issues related to the labeling review for Zelnorm.

BACKGROUND:

On February 11, 2000, Novartis Pharmaceuticals Corporation, submitted NDA 21-200 for the treatment of _____

in patients with irritable bowel syndrome (IBS) who identify _____
_____ constipation as their predominant symptoms”.

In a letter dated August 11, 2000, the Agency notified the sponsor that the new drug application was approvable. After reviewing the sponsor's response to the Approvable Letter, the Agency notified the sponsor in a letter dated June 15, 2001, that the application was not approvable.

On February 28, 2002, following discussions with the Agency, the sponsor submitted a complete response to the June 15, 2001 not approvable letter. This response contained additional safety data, a proposal for a risk management program, and revised labeling.

On June 19, 2002, the Agency met with the sponsor to discuss issues concerning the review of the application and proposed labeling for Zelnorm™.

THE CALL:

The sponsor's draft labeling, submitted June 26, 2002, was used as reference for discussion in this meeting (see attachment).

LABELING DISCUSSION

CONTRAINDICATIONS section

The sponsor expressed concern about the Agency's proposal : _____
_____ because this could potentially exclude many IBS patients. The sponsor proposed amending the restriction to include only patients with current symptoms of gallbladder disease. The sponsor also proposed to use the proposed mechanistic study to further clarify the risk to this patient population.

The sponsor was informed that the Agency is concerned about the use of Zelnorm in patients with a history of gallbladder disease because a syndrome exists where some patients develop stones after cholecystectomy, and removing the gallbladder does not alleviate the possibility that this event will occur. Furthermore, the proposed mechanistic study is not designed to answer the question concerning the risk to patients with a history of gallbladder disease. Therefore, until more is known about the effect of the drug on these patients, it is best to proceed with caution by contraindicating the use of Zelnorm in this patient population.

INDICATIONS AND USAGE section

The sponsor asked the Agency to further clarify its concerns about including information on the effect of Zelnorm on _____
_____ constipation in female patients.

The sponsor was informed that the Agency is concerned about potential marketing of Zelnorm to a broader patient population than IBS patients, such as patients with _____. The language proposed by the FDA helps to distinguish the use of Zelnorm in the treatment of IBS patients from patients with other abdominal conditions. The sponsor was also informed that the Agency considers the language in Rome Criteria II to be adequate for describing the symptoms for constipation predominant IBS patients.

The sponsor indicated that the medical community is moving away from the language in Rome II because of the focus of the language on constipation. The sponsor stated that it is concerned that primary physicians may misdiagnose patients by relying on the Rome II criteria. The sponsor proposed as an alternative, that the reference to constipation be changed to a "primary" instead of "predominant" symptom.

The sponsor was informed that, since IBS is a condition of exclusion. Including _____ in the indication does not increase the chance for correct diagnosis of IBS patients. Additional education for the physician in diagnosing and treating this form of IBS would most likely be a better way to increase the chance for correct diagnosis. The proposal for the use of "primary" instead of "predominant" would be considered. However, since the language about _____ is in other sections of the labeling, it is unlikely that the proposed change would be acceptable.

CLINICAL STUDIES section

The sponsor was requested to delete the proposed chart and reinstate the FDA proposed chart because the data in the FDA chart provided weekly information that might be useful to the physician in evaluating the use of Zelnorm for IBS patients. The sponsor's chart does not contain weekly data, and therefore, does not convey much clinically useful information and might be confusing to the treating physician.

The sponsor stated that adding the sponsor's chart provides the clinician with clinically relevant information for managing IBS patients. Including weekly data presents major issues in educating the physician. The sponsor asked that if the information about the secondary endpoints was not included in the labeling,

would the Agency object to the sponsor including it in educational materials used in the marketing of Zelnorm.

The sponsor was informed that it is unacceptable to include in educational materials to the physician, figures and charts based upon the secondary endpoints. Including the secondary endpoints in scientific journals might be acceptable.

The sponsor proposed to resubmit the original graph with the _____ added to the data.

The sponsor was informed that the original graph with the _____ added would be more confusing. In addition, problems with multiplicity in and across studies result in questions about the usability of the original graph because of the unreliability of the data. The FDA chart provides a clearer picture of the data.

The sponsor stated that it would discuss the matter further with Novartis' statistical team and continue dialogue on the subject with the Agency at a later date.

_____ section

The sponsor asked the Agency to explain why it proposes to delete the _____ section in the labeling.

The sponsor was informed that information contained in the _____ section was duplicated in the MECHANISM OF ACTION section of the labeling.

The sponsor asked whether the Agency would object to amending the wording in the MECHANISM OF ACTION section to include _____. The sponsor explained that _____ is the best description of the action of Zelnorm.

The sponsor was informed that the proposed language, "tegaserod has _____", is unacceptable because it might lead to off-label uses for indications such as _____. The Agency suggested the sponsor use the language in the currently proposed labeling or considers using _____ peristaltic : _____ as alternative language.

The sponsor stated that it does not intend to have off-label uses for Zelnorm, but is seeking to increase the education of the physician by providing the most accurate information about how the drug works. The sponsor indicated it would consider the Agency's comments and submit a proposal.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY section

The sponsor was informed that because the first test was positive, the second test had diminished results, and the third test involved a different strain altogether, the FDA proposed statement concerning the Ames test represents the most accurate description of the results. Therefore, the language proposed by the FDA in the labeling should remain.

The sponsor agreed to keep the FDA proposed language.

POST-MARKETING EXPERIENCE section

The sponsor asked for clarification of the term

The Agency and sponsor agreed to change the wording to “cholecystitis and increased transaminases”.

ADVERSE REACTIONS section

The sponsor was asked to clarify the number “2632” in the sentence “In phase 3 clinical trials in which 2632 patients received _____”

The sponsor stated that the number referred to the number of patients who participated only in the 3 studies (301, 351, and 358) involving the 6mg b.i.d. dosage of tegaserod.

GENERAL DISCUSSION

The sponsor was asked to submit proposals for post-marketing studies evaluating (1) the durability of response over a 12-week period and (2) the long-term effect of Zelnorm. The proposals should include evaluations of lower doses and/or intermittent drug dosing, have balanced variables, and include analyses of controlled groups vs. respondent groups. In addition, these proposals should include time frames for starting and completing the studies.

The sponsor agreed to submit the requested proposals and to work with the Agency to formulate final study protocols.

CONCLUSION

1. The sponsor agreed to consider the Agency's comments and re-submit draft labeling with the agreed upon changes and newly proposed revisions.
2. The sponsor agreed to submit proposals evaluating the durability of response over a 12-week period and the long-term effect of Zelnorm and to work with the Agency to formulate final study protocols.

**APPEARS THIS WAY
ON ORIGINAL**

Labeling Attachment:

**Confidential –
Not For Public Disclosure**

**APPEARS THIS WAY
ON ORIGINAL**

WITHHOLD 7 PAGE (S)

Draft

Labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM

DATE: July 16, 2002

FROM: Paul E. Levine, Jr., R.Ph.; Regulatory Health Project Manager *for*
Victor Raczkowski, M.D., M.Sc., Acting Division Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Additional Labeling Comments
NDA 21-200; Zelnorm™ (tegaserod maleate) Tablets

TO: Donna Vivelo, Associate Director, Drug Regulatory Affairs

Please refer to your July 12, 2002, submission of revised labeling for Zelnorm™ (tegaserod maleate) Tablets.

We further refer to our proposed labeling sent to you by facsimile on July 15, 2002, and to the meeting on July 16, 2002, in which FDA and representatives of Novartis met to discuss the proposed labeling revisions for Zelnorm.

In addition to the changes agreed upon in the meeting, we propose the following revision under the "How Should I Take Zelnorm?" section of the patient package insert:

Change:

- You should take Zelnorm twice a day _____, or as your doctor prescribes it."

To:

- You should take Zelnorm twice a day on an empty stomach, before a meal, or as your doctor prescribes it.

**APPEARS THIS WAY
ON ORIGINAL**

We request that you submit the revised patient package insert with the changes recommended above, as soon as possible.

If you would like to discuss the matter further, or if you have questions concerning the proposed revisions, you may contact me at (301) 443-8347.

BEST POSSIBLE COPY

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Paul Levine
7/16/02 09:50:34 AM
CSO

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF TELECON

DATE: JUNE 19, 2002

APPLICATION NUMBER: NDA 21-200, Zelnorm™ (tegaserod) Tablets

BETWEEN:

Novartis Pharmaceuticals Corporation

Martin Lefkowitz, M.D., Executive Director, Clinical Research & Development

David Earnest, M.D., Clinical Research Physician, Clinical Research & Development

James McLeod, MD, Executive Director, Clinical Pharmacology

Jean J Garaud, Global Head of CRD

Kurt Graves, Senior Vice-President and General Manager, US Commercial Operations

Mathias Hukkelhoven, Ph.D., U.S. Head of Regulatory Affairs

Donna Vivello, Associate Director, Drug Regulatory Affairs

Phone: (973) 781-3572

Representing: Novartis Pharmaceuticals Corporation

AND

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Victor Raczkowski, M.D., M.Sc., Acting Director

Joyce Korvick, M.D., M.P.H., Deputy Director

Hugo E. Gallo-Torres, M.D., Ph.D., Medical Team Leader, GI Drugs

Liang Zhou, Ph.D., Chemistry Team Leader

Paul E. Levine, Jr., R.Ph., Regulatory Project manager

Office of Drug Evaluation III (HFD-103)

Florence Houn, M.D., M.P.H., Director

Office of Clinical Pharmacology and Biopharmaceutics (OCPB), HFD-870

Suliman Al-Fayoumi, Ph.D., Biopharm Reviewer

Division of Biometrics II (HFD-715)

Edward Nevius, Ph.D., Division Director

Tom Permutt, Ph.D., Statistical Team Leader

Division of Surveillance, Research, and Communication Support, HFD-410

Jeanine Best, MSN, RN, PNP, Regulatory Health Project Manager

SUBJECT: To answer the sponsor's questions concerning the Agency's comments on the sponsor's proposed labeling.

BACKGROUND:

On February 11, 2000, Novartis Pharmaceuticals Corporation, submitted NDA 21-200 for the treatment of _____ in patients with irritable bowel syndrome (IBS) who identify _____ constipation as their predominant symptoms".

In a letter dated August 11, 2000, the Agency notified the sponsor that the new drug application was approvable because of concerns about the efficacy and safety of the drug. On December 15, 2000, the sponsor submitted a complete response to this approvable letter.

In a letter dated June 15, 2001, the Agency notified the sponsor that after review of the December 15, 2000, resubmission, the application was not approvable because the safety concerns for use of tegaserod outweighed the drug's effect.

On February 28, 2002, following discussions with Agency, the sponsor submitted a complete response to the June 15, 2001 not approvable letter. This response contained additional safety data, a proposal for a risk management program, and revised labeling for Zelnorm.

In a letter dated June 17, 2002, the Agency sent the sponsor comments concerning the proposed labeling.

THE CALL:

The attached labeling was used as reference for the discussion with the sponsor.

LABELING DISCUSSION

CONTRAINDICATIONS section

The sponsor asked what specific concerns the Agency had concerning the use of Zelnorm and which patients did the Agency seek to exclude from use of the drug.

The sponsor was informed that the Agency is concerned about use of the Zelnorm in patients with a history of biliary tree events and patients with moderately and severely impaired renal function. Until more is known about the adverse event profile, the Agency feels that the drug should be contraindicated in these patients.

INDICATIONS AND USAGE section

The sponsor asked if the Agency would consider retaining the phrase _____ as part of the indication. If the Agency disagreed, the sponsor asked if the Agency would consider alternative language containing similar indications.

The sponsor was informed that language as proposed by the Agency is consistent with the language in Rome Criteria II and represents an accurate description for use of Zelnorm. However, the Agency would consider the sponsor's alternative proposals.

The sponsor indicated that the Rome II criteria may not reflect what occurs in diagnosing and treating IBS in actual practice. Therefore, additional wording might be necessary to assist the physician in managing IBS patients.

The sponsor was informed that additional information to assist the physician in diagnosing and treating this form of IBS could probably be included in separate educational materials to the doctor and the patient.

CLINICAL STUDIES section

The sponsor asked for clarification about the Agency's revisions to the CLINICAL STUDIES section.

The sponsor was informed that the revisions were intended to reconcile the 4-week treatment data from the clinical trials with the information presented by the sponsor in the Clinical Studies section. The sponsor was also informed that the Agency acknowledges that the evidence for efficacy of Zelnorm is marginal and although the safety concerns for the drug have been mitigated, they have not been eliminated. As such the Agency continues to be concerned about the safety of the drug, the durability of the drug's effects, and that the drug's risk-benefit profile could be unfavorable if safety issues arise.

In addition, the sponsor was informed that data for 4 weeks and 12 weeks from all three studies should be included in the Clinical Studies section and not just data from the most favorable study. The sponsor was further informed that in view of the available data, Zelnorm would probably not be approved for _____

The sponsor asked if figures demonstrating the efficacy of Zelnorm for the secondary endpoint are acceptable.

The sponsor was informed that figures and charts based upon the secondary endpoints are unacceptable.

GENERAL DISCUSSION

The sponsor noted that the language in the labeling for proton pump inhibitors (PPIs) allowed the physician discretion in prescribing the drugs and asked if the Agency would consider a similar approach to the labeling for Zelnorm.

The sponsor was informed that the PPIs had maintenance and safety study data that supported the labeling for the drug. Zelnorm does not have the data to support similar labeling.

The sponsor was asked about Novartis' plans for direct-to-consumer (DTC) advertising.

The sponsor responded that there are no plans for DTC advertisements during the immediate launch period. Novartis would like to work with the Agency during the post-marketing period to evaluate the safety of the drug before initiating DTC advertisements.

The sponsor was informed that the Agency is very concerned about possible tachyphylaxis to the effects of Zelnorm and possible risks associated with use of the drug, including abdominal surgeries, and would like to receive evidence that the post-marketing surveillance system showed no serious adverse drug events before widespread advertisements to the public are initiated.

The sponsor stated that Novartis is committed to a responsible launch of Zelnorm that includes assuring that the drug is reasonably safe before initiating DTC advertisements.

The sponsor was asked to submit the following:

1. A proposal for studies to evaluate the durability of Zelnorm, including intermittent dosage studies, _____
2. A statistical analysis of weeks 7 through 11 in study #301 for "Complete Considerable Relief" by week

The sponsor agreed to submit the requested information and would consider the Agency's comments in submitting revised labeling.

The call was ended.

**APPEARS THIS WAY
ON ORIGINAL**

WITHHOLD 16 PAGE (S)

Draft

Labeling

MEMORANDUM OF TELECON

DATE: June 11, 2001

APPLICATION NUMBER: NDA 21-200, Zelnorm™ (tegaserod) Tablets

BETWEEN:

Name: Thomas Koestler, Ph.D.; Global Head of Regulatory Affairs.
Matthew Hukkelhoven; U.S. Regulatory Affairs
Adrian Birch; Executive Director, Regulatory Affairs
Donna Vivello; Associate Director, Regulatory Affairs
Martin Lefkowitz, M.D., Executive Director, Clinical Research
Yingqi Shi, Ph.D., Project Biostatistician
Phone: (973) 781-3572
Representing: Novartis PharmaG Basel, Switzerland

AND

Name: Julieann DuBeau, RN, MSN; Chief, Project Management Staff
Florance Houn, M.D., M.P.H., F.A.C.P.; ODE III Director

Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Information Requests for Pending NDA 21-200

BACKGROUND INFORMATION:

Novartis PharmaG Basel, Switzerland has a pending NDA for Zelnorm™ (tegaserod) Tablets with the proposed following indication: Treatment of constipation-predominate irritable bowel syndrome (IBS-C) in female patients.

TODAY'S PHONE CALL:

The firm was requested to provide the information contained in the attachment to this memorandum by 8AM, on June 13, 2001 (see attachment). Regarding request #5 in the attachment, tables from pages 48-51 of the Medical Officer review dated June 8, 2001, were provided to the firm. The firm was requested to add a chief complaint column to these tables.

The firm stated they would provide the Agency with a letter asking for consideration of a short term indication for IBS-C as well as other options. Dr. Houn stated that the letter should include how compliance with a short-term labeled indication would be ensured given that the drug has outstanding safety concerns. The telephone conversation was then concluded.

FOLLOW-UP:

The attachment and the tables referenced above were faxed to the firm on June 11, 2001.

Julieann DuBeau, RN, MSN
Chief, Project Management Staff

Questions for Novartis about Zelnorm:

- 1) During the baseline period for clinical trials 358, 301, and 307 provide the descriptive variables that describe subjects' IBS disease (such as duration of disease, frequency of stools, consistency of stools, etc.). Present the data for drug arm and placebo arm for each trial with n, mean, median, range and SE.
- 2) Please provide sub-analyses from clinical trials 358, 301, 307 of drug versus placebo for primary efficacy variable for elderly (equal to or greater than 65 years of age) and any abdominal/pelvic surgery (lap or open); provide the same data for Blacks and Others. Provide denominators.
- 3) Provide a table that includes data from all efficacy phase 3 studies (358, 351, 301, and 307) for QT changes in females and males for drug arm-12mg and placebo arm. Provide mean change, max, minimum, and standard error for each sex.
- 4) Provide a table that includes data from all efficacy phase 3 studies for drug arm-12mg and placebo in females and males of dizziness, syncope, palpitations, irregular heartbeat, chest pains, lightheadedness, and other symptoms that may reflect arrhythmia. Provide information for total % and each symptom % for each sex.
- 5) Provide a table using all safety data that lists the chief complaint/presenting complaint of cases (such as pain, fever, loss of consciousness, etc.) that went to surgery for drug and placebo arm. If no chief complaint, state so. Provide age, sex, dose, study/subject no., adverse event, surgical procedure/comments (as provided in prior submission), day of surgery.
- 6) ! ~~_____~~

APPEARS THIS WAY
ON ORIGINAL

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Julieann DuBeau
6/11/01 04:50:44 PM
CSO

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF TELECON

DATE: MAY 24, 2001

APPLICATION NUMBER: NDA 21-200, ZELNORM™ (tegaserod) TABLETS

BETWEEN:

Name: Donna M. Vivello, Associate Director, Drug Regulatory Affairs
Cathy Ford, Associate Director DRA-CMC
Phone: (973) 781-3572
Representing: Novartis Pharmaceuticals Corporation

AND

Name: Paul E. Levine, Jr., R.Ph., Regulatory Project Manager
Liang Zhou, Ph.D., Chemistry Team Leader
Raymond Frankewich, Ph.D., Chemistry Reviewer
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Requests for additional information

BACKGROUND:

Novartis Pharmaceuticals Corporation, submitted this NDA on February 11, 2000, intended for the treatment of _____

_____ patients with irritable bowel syndrome (IBS) who identify _____
_____ constipation as their predominant symptoms.

In a Deficiency (DR) letter dated July 24, 2000, the sponsor was notified of several Chemistry, Manufacturing, and Controls (CMC) deficiencies concerning the drug substance and drug product. On August 01, 2000, the sponsor submitted data and other information in response to this DR letter.

In a letter dated August 11, 2000, the firm was notified that the application was found approvable due to concerns about the efficacy and safety of the drug. On December 15, 2000, the sponsor submitted a complete response to the approvable letter. In addition, on December 20, 2000, the sponsor submitted a CMC amendment to the NDA.

In a letter dated March 18, 2001, the sponsor was requested to provide additional information concerning the drug substance and drug product. The sponsor responded to this request in a submission dated April 27, 2001.

The call is intended to discuss unresolved CMC issues.

THE CALL:

The sponsor was asked to provide the following information:

Drug Substance Comments

┌

Drug Product Comments

┌

The sponsor agreed to provide a _____
_____ The sponsor further agreed to provide _____
_____ In addition, the firm agreed to
provide the requested information for the other items, if possible. However, the firm

expressed concern that submission of all of the information may not be possible by the action due date.

The Chemistry Team Leader indicated that the sponsor should provide all available information as soon as possible. A determination of the completeness of the information would be made after the CMC review of the submission. If the information is submitted in time to allow a review before the action due date, then the sponsor would be notified whether the submission is sufficient for an action or requires a commitment for additional information, or if additional information would be needed before approval.

The call was ended

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Paul Levine
6/8/01 01:02:34 PM
CSO

Liang Zhou
6/8/01 01:12:57 PM
CHEMIST

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-200

INFORMATION REQUEST LETTER

Novartis Pharmaceuticals Corporation
Attention: Donna M. Vivello
Associate Director Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. Vivello:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tegaserod hydrogen maleate tablets.

We also refer to your submissions dated August 01, December 15 and 20, 2000.

We are reviewing the Chemistry Manufacturing and Controls, and the Pharmacology sections of your submissions and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

CHEMISTRY

Drug Substance

┌

Drug Product

┌

┌

┌

PHARMACOLOGY

1. Provide the following information for study #RD-2000-02503, entitled "Investigations on the 5-HT4 receptor status of human appendix and non-GI abdominal and pelvic organs compared to human intestinal samples":
 - a. 5-HT4 receptor mRNA data for the tissues collected from all ten patients
 - b. numerical data for each patient and group (i.e., mean values with standard deviations or standard errors for each sex and both sexes)
2. Define the unit of expression of 1.0 used for 5-HT4 receptor mRNA in the liver.

If you have any questions, call Paul E. Levine, Jr., R.Ph., Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

{See appended electronic signature page}

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Hugo Gallo Torres

3/29/01 06:33:58 PM

Signing for Lilia Talarico, M.D., Division Director

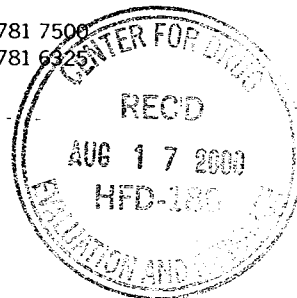
**APPEARS THIS WAY
ON ORIGINAL**



COPY 2

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325



August 14, 2000

Lilia Talarico, MD, Director
Division of Gastrointestinal and
Coagulation Drug Products/HFD-180
Office of Drug Evaluation III
Attn: Document Control Room 6B-24
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

NDA No. 21-200

Zelmac™ [tegaserod maleate] Tablets

NEW CORRESP

Dear Dr. Talarico:

We refer to our NDA 21-200 for Zelmac™ (tegaserod maleate) tablets which was submitted on February 11, 2000. We also specifically refer to your August 11, 2000 action letter which designates the NDA as approvable and requests that additional data regarding the efficacy and safety of Zelmac be submitted prior to the approval of the application.

At this time we are notifying you of our intent to file an amendment to the application in order to satisfy the concerns outlined in your August 11th correspondence. We will remain in contact with your Division such that we may agree on the content and format of the foreseen amendment.

Please feel free to contact the undersigned at 973-781-3572 with regard to any matter relating to this application.

Sincerely,

Donna M. Vivello
Associate Director
Drug Regulatory Affairs

DV/
Submitted in duplicate

**APPEARS THIS WAY
ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT NOVARTIS PHARMACEUTICALS CORPORATION		DATE OF SUBMISSION AUGUST 14, 2000
TELEPHONE NO. (Include Area Code) (973) 781-3572		FACSIMILE (FAX) Number (Include Area Code) (973) 781-3590
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 59 Route 10 East Hanover, New Jersey, 07936-1080		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-200		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) tegaserod maleate	PROPRIETARY NAME (trade name) IF ANY Zelmac™	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) 3-(5-methoxy-1H-indol-3-ylmethylene)-N-pentylcarbazimidamide hydrogen maleate		CODE NAME (If any) HTF 919
DOSAGE FORM Tablet	STRENGTHS 2 mg and 6 mg	ROUTE OF ADMINISTRATION Oral
(PROPOSED) INDICATION(S) FOR USE: Irritable bowel syndrome (IBS)		

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)	
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b) (1) <input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 507	
IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug Holder of Approved Application	
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> SUPAC SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER	
REASON FOR SUBMISSION General Correspondence	
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)	
NUMBER OF VOLUMES SUBMITTED 1	THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Application, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (Check all that apply)

1. Index	
2. Labeling (check one)	<input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
3. Summary (21 CFR 314.50 (c))	
4. Chemistry section	
A. Chemistry, manufacturing, and control information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)	
B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)	
5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)	
6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)	
7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))	
8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)	
9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)	
10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)	
11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)	
12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)	
13. Patent information on any patent which claims the drug (21 U.S.C 355 (b) or (c))	
14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))	
15. Establishment description (21 CFR Part 600, if applicable)	
16. Debarment certification (FD&C Act 306 (k) (1))	
17. Field copy certification (21 CFR 314.50 (k) (3))	
18. User Fee Cover Sheet (Form FDA 3397)	
19. OTHER (Specify)	

CERTIFICATION


I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606 and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact law.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Donna Vivello, Associate Director Drug Regulatory Affairs	DATE 8/14/2000
---	--	-------------------

ADDRESS (Street, City, State, and ZIP Code) 59 Route 10 East Hanover, New Jersey, 07936-1080	Telephone Number (973) 781-3572
--	------------------------------------

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.



DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 21-200

Food and Drug Administration
Rockville MD 20857

DISCIPLINE REVIEW LETTER

Novartis Pharmaceuticals Corporation
Attention: Donna Vivelo
Associate Director Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

JUL 24 2000

Dear Ms. Vivelo:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zelmac™ (tegaserod hydrogen maleate) Tablets.

Our review of the Chemistry, Manufacturing, and Controls (CMC) section of your submission is complete, and we have identified the following deficiencies:

Drug Substance

└

└

WITHHOLD 5 PAGE (S)

Labeling

Regarding your package insert submitted March 16, 2000, (received March 22, 2000), and your labels submitted May 5, 2000, (received May 8, 2000):

1. Provide a statement in the DESCRIPTION section of the package insert-describing the 2mg tablet.
2. Add the words "tegaserod — maleate" on the carton label which will hold the blister cards on the unit-dose blisters.
3. Replace the word — with the words — , throughout the package insert and labels. If necessary, the sizes of the lettering in which the proprietary and non-proprietary names appear should be changed in order to comply with the act.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-200

Page 8

If you have any questions, call Paul E. Levine, Jr., R.Ph., Regulatory Project Manager, at (301) 827-7310.

Sincerely,

/s/

Liang Zhou, Ph.D.

Chemistry Team Leader for the

Division of Gastrointestinal and

Coagulation Drug Products, (HFD-180)

DNDC II, Office of New Drug Chemistry

Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

NDA 21-200

JUL 17 2000

Novartis Pharmaceuticals
Attention: Donna M. Vivello
Associate Director
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. Vivello:

We acknowledge receipt on July 03, 2000, of your June 28, 2000, correspondence requesting a meeting to discuss the resolution of outstanding issues, including labeling discussions for your pending application. We have concluded that a meeting is unnecessary since the reviews have not been completed and there are no outstanding issues at this time.

If you disagree that a meeting is not necessary, we encourage you to discuss the matter with Paul E. Levine, Jr., R.Ph., Regulatory Project Manager, of this division. If the issue can not be resolved at the division level, you may formally request reconsideration of the matter at the office level after providing the division an opportunity to review any materials you intend to rely on in an appeal to Florence Houn, M.D., M.P.H., F.A.C.P., Director, Office of Drug Evaluation III. A copy of any appeal should be sent to this division.

If you have any questions, contact Paul E. Levine, Jr., R.Ph., Regulatory Project Manager, at (301) 827-7310.

Sincerely,

/S/
7-17-00

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

LEVINE

MEMORANDUM OF TELECON

DATE: MARCH 8, 2000

APPLICATION NUMBER: NDA 21-200 ZELMAC™ (tegaserod)

BETWEEN:

Name: Donna M. Vivel, Associate Director, Drug Regulatory Affairs

Phone: (973) 781-3572

Representing: Novartis Pharmaceuticals Corporation

AND

Name: Paul E. Levine, Jr., R.Ph., Regulatory Project Manager

Hugo Gallo-Torres, M.D., Medical Team Leader

Raymond Joseph, M.D., Medical Reviewer

Division of Gastrointestinal and Coagulation Drug Products, HFD-180
and

Khairy Malek, M.D., Division of Scientific Investigations (HFD-45)

SUBJECT: Requests for additional information

BACKGROUND:

Novartis Pharmaceuticals Corporation, submitted this NDA on February 11, 2000, (received February 11, 2000) for Zelmec™ (tegaserod) Tablets with the following proposed indication: for the treatment of _____

_____ in patients with irritable bowel syndrome (IBS) who identify _____ constipation as their predominant symptoms. On March 7, 2000, a 45-day Filing Meeting was held to determine the fileability of the application.

THE CALL:

The firm was notified that the application will be presented to a Gastrointestinal Advisory Committee. A meeting date in late June 2000, has been requested, but has not yet been confirmed. The firm will be notified of the date when confirmed. In response to information requested in the filing meeting by the reviewers, Ms. Vivel was asked to provide the following information:

1. A statement that all manufacturing facilities are ready for inspection.
2. The unannotated package insert on diskette.
3. A layout of the immediate container and carton labels.

4. A statement certifying that all information contained on CDROM are identical to the information contained in the paper submission.
5. Safety and stability data on diskette, or the location if already submitted.

In addition, requests from the clinical reviewer were made following the Filing meeting. In response to these requests, Ms. Viveló was requested to provide the following information.

1. A comprehensive list of all clinical sites, including investigators, the number of patients per site, and location for studies B301, B307, and B351. The requested information should be listed according to study number.
2. Provide the hospital discharge summary, surgery and pathology reports, and any follow up reports for all patients diagnosed with ovarian cysts while taking the drug or placebo.

Ms. Viveló agreed to provide the information as requested. She stated that she would make inquiries as to whether the stability and animal tumorigenicity has been provided, and if so, where they can be found in the application. She further stated that after consultation with the appropriate personnel, she would either provide the exact locations of the requested information, or submit it to the NDA. Ms. Viveló indicated that she would call me back with a date for the submission of the requested information.

The call was concluded.

Follow-Up:

In a telephone conference on March 17, 2000, Ms. Viveló was requested to submit a statement certifying that the carcinogenicity information submitted to IND — is identical to that submitted in NDA 21-200.

3/20/00
/S/

Paul E. Levine, Jr., R.Ph.
Regulatory Project Manager

**APPEARS THIS WAY
ON ORIGINAL**

Memorandum of Meeting Minutes

Meeting Date: July 16, 2002
Meeting Time: 8:30-10:00pm
Meeting Location: Conference Room M, PKLN Bldg., 3rd Floor

Application Number: NDA 21-200, Zelnorm™ (tegaserod) Tablets

Type of Meeting: Type C, Industry Meeting
Meeting Chair: Florence Houn, M.D., M.P.H.
Meeting Recorder: Paul E. Levine, Jr., R.Ph.

List of FDA Attendees

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Victor Raczowski, M.D., M.Sc., Acting Director
Joyce Korvick, M.D., M.P.H., Deputy Director
Hugo E. Gallo-Torres, M.D., Ph.D., Medical Team Leader, Gastrointestinal Drugs
Gary J. Della'Zanna D.O. M.Sc., Medical Reviewer
Paul E. Levine, Jr., R.Ph., Regulatory Project manager

Office of Drug Evaluation III (HFD-103)

Florence Houn, M.D., M.P.H., Director

Division of Drug Risk Evaluation, (HFD-440)

Julie Beitz, M.D., Division Director

Division of Biometrics II (HFD-715)

Edward Nevius, Ph.D., Division Director
Tom Permutt, Ph.D., Statistical Team Leader

Division of Surveillance, Research, and Communication Support, HFD-410

Jeanine Best, MSN, RN, PNP, Regulatory Health Project Manager

Division of Drug Marketing, Advertising, and Communications, HFD-42

Marci Kiester, Pharm.D., Senior Regulatory Review Officer

External Constituent Attendees:

Novartis Pharmaceuticals Corporation

Martin Lefkowitz, M.D., Executive Director, Clinical Research & Development
David Earnest, M.D., Clinical Research Physician, Clinical Research & Development
Kurt Graves, Senior Vice-President and General Manager, US Commercial Operations
Mathias Hukkelhoven, Ph.D., U.S. Head of Regulatory Affairs

Gregory Ligozio, Project Statistician, Biostatistics
Fanny Ki, Ph.D., Associate Director, Biostatistics
Chin Koerner, Regulatory Liaison Office
John Cutt, Ph.D., Associate Director, Drug Regulatory Affairs
Donna Vivelo, Associate Director, Drug Regulatory Affairs

BACKGROUND

On February 11, 2000, Novartis Pharmaceuticals Corporation submitted NDA 21-200 for the treatment of _____ patients with irritable bowel syndrome (IBS) who identify _____ constipation as their predominant symptoms”.

In a letter dated August 11, 2000, the Agency notified the sponsor that the new drug application was approvable. After reviewing the sponsor's response to the Approvable Letter, the Agency notified the sponsor in a letter dated June 15, 2001, that the application was not approvable.

On February 28, 2002, following discussions with the Agency, the sponsor submitted a complete response to the June 15, 2001 not approvable letter. This response contained additional safety data, a proposal for a risk management program, and revised labeling.

On June 19, 26; and July 03, and 10, 2002, the Agency met with the sponsor to discuss issues concerning the review of the application and proposed labeling for Zelnorm™.

On July 12, 2002, the sponsor submitted draft labeling in response to the Agency's comments in the July 10, 2002, meeting.

MEETING OBJECTIVE

To provide comments on the sponsor's proposed labeling submitted July 12, 2002.

DISCUSSION

The sponsor's draft labeling, submitted July 12, 2002, was used as a reference for discussion in this meeting (see attachment 1).

The sponsor provided a handout containing new text for lines 133 to 146 under the CLINICAL STUDIES section of the prescriber information insert (see attachment 2).

LABELING DISCUSSION

Information For The Patient Insert

The sponsor proposed the following revisions under the *What are the possible side effects of Zelnorm?* section.

Line 48: add the statement "*If you get different or worse abdominal pain while using Zelnorm, call your doctor.*"

Line 50: add the statement : _____

The Agency found these proposed additions acceptable.

Prescriber Information Insert

The Agency requested that the sponsor delete the sentences on lines 118 – 120 under the CLINICAL STUDIES section

The sponsor proposed to revise the sentences to read "*The differences in response rates vs. placebo were greater at month 1 than month 3.*"

The Agency found this revision acceptable.

The Agency requested that the sponsor revise the sentence on lines 124 – 125 under the CLINICAL STUDIES section to include a statement about complete relief, considerable relief, and somewhat relief.

The sponsor proposed to revise the statement to read "*The proportion of patients with complete, considerable or somewhat relief at weeks 1,4,6,8 and 12 are shown in the figure below.*"

The Agency found this revision acceptable.

The sponsor proposed to revise lines 133 – 146 under the CLINICAL STUDIES section to the text written in the handout (see attachment 2).

The Agency found this change acceptable.

MARKETING PROCESS

Dr. Houn asked the sponsor to clarify what is meant by "early launch" of Zelnorm.

The sponsor stated that "early launch" refers to a period between 4 to 6 months post-approval of Zelnorm.

Dr. Houn asked when Novartis expects to have the drug available to patients in the United States.

The sponsor stated that the drug would be available sometime during the first week of September, 2002.

Dr. Houn asked if Novartis has contacted or plans to contact the various gastrointestinal interest groups concerning the marketing of Zelnorm. This would be a good opportunity to educate the medical community about the risks and benefit of the drug.

The sponsor stated that there are no plans to contact the gastrointestinal interest groups other than the usual information about the release of the new drug to the market. However, the sponsor would consider contacting these groups and include more educational materials about Zelnorm.

Dr. Houn stated that the Agency plans to have a talk paper and Dr. Korvick will be the spokesperson.

The sponsor asked if the Agency would be willing to share the contents of the talk paper with the sponsor prior to releasing it to the press.

Dr. Houn stated that the Agency does not usually share its talk papers with the sponsor, but the Agency would provide Novartis with the action letter prior to releasing information to the press. Dr. Houn further stated that it is acceptable for the sponsor to submit a copy of its press release to the Agency prior to the action, if the sponsor wishes.

CONCLUSION

The Sponsor will submit a labeling amendment that contains the agreed upon changes in text to the Prescriber Information insert and the Information For The Patient insert.

Attachments:

**APPEARS THIS WAY
ON ORIGINAL**

WITHHOLD 15 PAGE (S)

Draft

Labeling

Clinical Studies section

(Lines 133 to 146)

In addition, individual symptoms of abdominal pain/discomfort and bloating were assessed daily using a 6 or 7 point intensity scale. A positive response was defined as at least a 1 point reduction in the scale. During the first four weeks in the fixed dose studies, 8 – 11 % more Zelnorm-treated patients than placebo patients were responders for abdominal pain/discomfort. Similarly, 9-12% more Zelnorm-treated patients were responders for bloating. Corresponding differences at month 3 were 1-10% for abdominal pain/discomfort and 4-11% for bloating. Patients on Zelnorm also experienced an increase in median number of stools from 3.8/week at baseline to 6.3/week at month 1 and 6.0/week at month 3, while placebo patients increased from 4.0/week to 5.1/week at month 1 and 5.5/week at month 3.

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Florence Houn
8/2/02 05:07:42 PM

**APPEARS THIS WAY
ON ORIGINAL**

Mathias Hukkelhoven, PhD
Sr. Vice President, Global Head
Drug Regulatory Affairs

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973-781-6035
Fax 973-781-5544
Internet: mathias.hukkelhoven@pharma.novartis.c

July 9, 2002

Victor Raczkowski, MD, Acting Director
Division of Gastrointestinal and
Coagulation Drug Products/HFD-180
Office of Drug Evaluation III
Attn: Document Control Room 6B-24
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857


NDA No. 21-200
Zelnorm™ [tegaserod maleate] Tablets

Proposed Labeling Revisions

Dear Dr. Raczkowski:

We refer to our pending New Drug Application for Zelnorm (tegaserod maleate) tablets and specifically to our ongoing labeling discussions regarding the physician package insert. We believe that we have made significant progress toward completing these discussions and look forward to finalizing the package insert pending the resolution of the remaining few issues outlined below. In preparation for our next teleconference on Wednesday, July 10th, we are submitting the attached proposed revisions in accordance with the agreements made during the July 3rd teleconference.

CLINICAL STUDIES Section:

We continue to feel strongly that the justifications put forth in our submission dated July 1, 2002 regarding the importance of including the weekly SGA of relief data in the Clinical Studies section of the package insert provides meaningful information for physicians and is consistent with recent FDA guidance on prescription drug labeling. In your response to us during the July 3rd teleconference you informed us that the bar chart presentation of the data (Alternative 2) was preferred over the  (Alternative 1). We agree with the Agency that this bar chart presentation does not overstate the results as was one of the primary concerns over inclusion of these data. It was requested that we add the data for weeks 8 and 12 to the presentation for the Agency's further review. These data are now included in the attached revised version of the package insert. If you prefer the bar chart from our submission of July 1st (1, 4 and 6 week data) we are prepared to include that one in the package insert. Once again we feel that these data complement the monthly analyses and provide a more complete view of the efficacy of tegaserod.

We were also requested to revise the text in the paragraph immediately following the above bar chart (lines 141 to 146) which described the observed effects of tegaserod on several of the secondary efficacy variables. Novartis has revised this paragraph accordingly. The data to support this revised text is provided in Attachment 1.

ADVERSE EVENTS Section:

The Agency requested that we review the data and clarify the statement in this section describing the nature of the diarrhea observed in patients on tegaserod. We therefore have revised this text to more clearly describe the diarrhea reported in the Phase 3 clinical studies; the supporting data is included in Attachment 1.

Patient Package Insert

As we agreed during the July 3rd teleconference, Novartis has revised the proposed text for the patient package insert to be consistent with the physician package insert. The revised patient package insert is attached for your review.

Phase IV Commitments

Novartis commits to conducting the following Phase IV studies:

1. A randomized, double-blind, crossover, placebo-controlled study to assess the effects of tegaserod 6 mg bid on gallbladder motility and biliary tract diameter in healthy volunteers and of tegaserod 6 mg bid and tegaserod 12 mg bid on gallbladder motility and biliary tract diameter in female patients with IBS-C, as submitted February 28, 2002 (Gallbladder mechanistic study).

Protocol Submission (with amendment for 12 mg bid cohort): February 2002

Study Start: Ongoing

Final Report Submission: First Quarter 2003

2. Zelnorm Epidemiological Study, a prospective cohort postmarketing surveillance study, to evaluate the frequency of gallbladder surgeries and other abdominal and pelvic surgeries and procedures, as submitted February 28, 2002.

Protocol Submission: September 2002

Study Start: Third Quarter 2002

Final Report Submission: Third Quarter 2005

3. A randomized, double-blind, parallel group, placebo-controlled study to evaluate the intermittent and/or long-term efficacy of Zelnorm.

Protocol Submission: October 2002

Study Start: Second Quarter 2003

Final Report Submission: First Quarter 2005

It is anticipated that the design of the latter study would be discussed with the Agency in advance of the October protocol submission. Novartis is considering

During the July 3rd teleconference, the Division raised potential concerns regarding the possible early initiation of Direct to Consumer (DTC) advertising for Zelnorm following receipt of marketing approval for Zelnorm. As Novartis communicated, we understand FDA's perspective on early DTC for Zelnorm and we are fully committed to maintaining our ongoing collaboration with FDA on matters relating to Zelnorm.

It is in the spirit of understanding and our continued cooperation with FDA that we indicated our intent not to initiate DTC for Zelnorm during the initial launch phase for the product. During this early launch phase we propose the following as the basis of mutual understanding moving forward:

1. During the early launch phase Novartis will closely monitor adverse events reported domestically and in the worldwide safety databases.
2. If Novartis intends to initiate DTC for Zelnorm we will proactively share our intent with FDA in advance of any formal DDMAC submission.
3. In initiating any DTC advertising for Zelnorm, we intend to comply with the existing regulatory framework (21 CFR 202.1) and DDMAC process relating to prescription drug promotion and advertising. We would expect that, should the Division wish to have greater involvement in any DTC advertising, it would collaborate with DDMAC in its review of any DTC materials submitted by Novartis for preclearance. We do not believe that any additional extraordinary measures beyond the foregoing (which already exceed those required by regulation) are necessary to address the issues raised by the Division.

We look forward to our discussion at the next scheduled teleconference on July 10th. Should you have any questions or concerns regarding this submission, please contact Donna Vivelo, Associate Director, Drug Regulatory Affairs at 973-781-3572.

Sincerely,

Mathias Hukkelhoven, Ph.D.
Sr. Vice-President, Global Head
Drug Regulatory Affairs

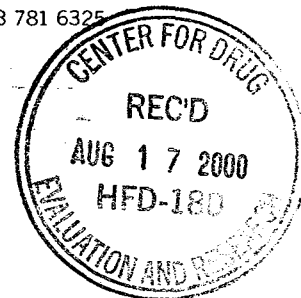
Desk Copy:
Dr. F. Houn
Dr. V. Raczkowski
Dr. Joyce Korvick
Dr. Hugo-Gallo-Torres
Mr. Paul Levine

**APPEARS THIS WAY
ON ORIGINAL**



Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325



August 15, 2000

Lilia Talarico, MD, Director
Division of Gastrointestinal and
Coagulation Drug Products/HFD-180
Office of Drug Evaluation III
Attn: Document Control Room 6B-24
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

NDA No. 21-200
Zelmac™ [tegaserod maleate] Tablets

NEW CORRESP

C

Dear Dr. Talarico:

We refer to our NDA 21-200 for Zelmac™ (tegaserod maleate) tablets which was submitted on February 11, 2000 and has been deemed approvable as per your August 11, 2000 correspondence.

At this time we are submitting the final minutes to our 90-day conference which took place on May 8, 2000. Please forward a copy of the Division's final minutes, when they are available. Please feel free to contact the undersigned at 973-781-3572 with regard to any matter relating to this application.

Sincerely,

Donna M. Vivel
Associate Director
Drug Regulatory Affairs

DV/
Attachments
Submitted in duplicate

APPEARS THIS WAY
ON ORIGINAL

This application contains the following items: (Check all that apply)

- | | | |
|---|---|---|
| 1. Index | <input type="checkbox"/> Draft Labeling | <input type="checkbox"/> Final Printed Labeling |
| 2. Labeling (check one) | | |
| 3. Summary (21 CFR 314.50 (c)) | | |
| 4. Chemistry section | | |
| A. Chemistry, manufacturing, and control information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2) | | |
| B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request) | | |
| C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2) | | |
| 5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2) | | |
| 6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2) | | |
| 7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4)) | | |
| 8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2) | | |
| 9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2) | | |
| 10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2) | | |
| 11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2) | | |
| 12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2) | | |
| 13. Patent information on any patent which claims the drug (21 U.S.C 355 (b) or (c)) | | |
| 14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A)) | | |
| 15. Establishment description (21 CFR Part 600, if applicable) | | |
| 16. Debarment certification (FD&C Act 306 (k) (1)) | | |
| 17. Field copy certification (21 CFR 314.50 (k) (3)) | | |
| 18. User Fee Cover Sheet (Form FDA 3397) | | |
| 19. OTHER (Specify) | | |

CERTIFICATION

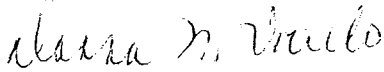
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606 and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact law.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Donna Vivalo, Associate Director Drug Regulatory Affairs	DATE 8/15/2000
---	---	-------------------

ADDRESS (Street, City, State, and ZIP Code) 59 Route 10 East Hanover, New Jersey, 07936-1080	Telephone Number (973) 781-3572
--	------------------------------------

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

FDA Meeting Minutes**May 8, 2000****Division of Gastrointestinal and Coagulation Drug Products (HFD-180)****Zelmac™ (tegaserod)****90-Day Conference****NDA 21-200**

Author(s): Donna Vivello
Document type: FDA Meeting Minutes
Document status: Final
Release date: 7-Jul-00
Number of pages: 5

Property of Novartis Pharma AG
Confidential

May not be used, divulged, published or otherwise disclosed
without the consent of Novartis Pharma AG

Meeting Participants: May 8, 2000

FDA Representatives:

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Florence Houn, M.D., Office Director
Lilia Talarico, M.D., Division Director
Steven Aurecchia, M.D., Deputy Division Director
Hugo Gallo-Torres, M.D., GI Medical Team Leader
Raymond Joseph, M.D., Medical Reviewer
Jasti Choudry, Ph.D., Pharmacology Team Leader
Ke Zhang, Ph.D., Pharmacology Reviewer
Liang Zhou, CMC Team Leader
Julie DuBeau, Regulatory Health Project Manager
Paul Levine, Jr., R.Ph., Regulatory Health Project Manager

Division of Pharmaceutical Evaluation, HFD-870

Suresh Doddapaneni, Ph.D., Biopharmaceutics Team Leader/Reviewer

Division of Biometrics II, HFD-715

Tom Permutt, Ph.D., Statistical Team Leader
Sonia Castillo, Ph.D., Statistical Reviewer

Novartis Representatives

Tom Koestler, Ph.D., Global Head, DRA
Russ Hume, Regulatory Liaison, DRA
Lawrence Hauptman, Ph.D., Director, DRA
Martin Lefkowitz, M.D., Director, Clinical Research
Peter Rueegg, M.D., Sr. Clinical Research Physician, Clinical Research
James McLeod, M.D., Executive Director, Clinical Pharmacology
Yann-Tong Chiang, Ph.D., Associate Director, Biostatistics
Yingqi Shi, Ph.D., Senior Statistician, Biostatistics
Philip Bentley, Ph.D., Preclinical Safety
Adrian Birch, Executive Director, CME, DRA
Cathy Ford, Associate Director, DRA CMC
Donna Vivello, Associate Director, DRA
Lisa Pitt, Pharm.D., Assistant Director, DRA

Consultants to Novartis

[]

Background

Novartis submitted a New Drug Application on February 11, 2000 which has been designated with Priority Review Status. The GI Division has indicated that they will bring Zelmac up for

review by the GI Advisory Committee on June 26, 2000. A draft briefing package for the Advisory Committee members was submitted on April 20, 2000 for the Division's review. This meeting was held to discuss the status of the Division's review and their comments on the draft briefing documentation.

Summary

The Agency indicated that the incidence of ovarian cysts in both the 2-year rat study and the clinical program is a safety review issue which needs to be addressed in our Advisory Committee presentation. Additional information was also requested to support the mechanistic theory for the incidence of adenocarcinoma/hyperplasia in the mouse.

The display of _____ in the draft briefing book, as well as _____ was discouraged by the Division, however Novartis indicated a desire to retain these displays in a separate section of the briefing documentation as they are considered to be informative for the Advisory Committee members. Novartis agreed to consider the inclusion of weekly analyses, possibly along with the monthly analyses already contained in the briefing documentation.

Proceedings

The meeting was divided into two main parts. First, the status of reviews by disciplines were discussed, followed by a point-by-point review of the 12 questions/comments issued to us by FDA regarding the draft Advisory Committee briefing documentation (see attachment 1).

Status of reviews

Pharmacology/Toxicology: Dr. Choudry noted the incidence of ovarian cysts in the 2-year carcinogenicity study. Given the occurrence of a few ovarian cysts in the clinical program, Dr. Choudry was concerned that there is an endocrinological mechanism behind the rat findings which could be relevant to humans. He requested that we separate the observed ovarian cysts into follicular vs. luteal, and run statistical analyses for each category. Dr. Choudry indicated that he would like to complete his review in about three weeks, and this information is requested as soon as possible.

Dr. Choudry also noted the incidence of adenocarcinoma in the mouse and our theoretical mechanism whereby a decrease in diamino oxidase (DAO) leads to an increase in polyamine which in turn stimulates hyperplasia and possibly tumor formation. He was interested in seeing the effect of pentylaminoguanidine (PAG) on hyperplasia in the mouse.

Chemistry, Manufacturing and Controls: Dr. Zhou indicated that the review is pending and that there are no outstanding issues at this time. Post-meeting note: The reviewer will accept the 9-month stability report on child-resistant blisters at the end of May, without affecting the review time clock.

Biopharmaceutics: Dr. Doddapaneni indicated that the review is ongoing. He noted the presystemic metabolism of tegaserod and the metabolites M29 and M7. He specifically asked

whether we could provide more information on the enzyme that mediates the formation of M7.

Clinical: Dr. Raymond Joseph mentioned the imbalance of ovarian cysts in women on tegaserod (4) vs. placebo (1). He asked whether there were any additional ovarian cysts reported, and we indicated that there have been none.

Dr. Joseph also asked whether we had collected any information on menstruation. Dr. Lefkowitz responded that we had only collected the last menses prior to starting the study. Dr. Joseph was also interested in the prevalence of PID or endometriosis in study patients, and whether we ruled this out prior to study entry. Dr. Lefkowitz indicated that a history of PID or endometriosis did not exclude the patient as long as the condition was not active.

Dr. Joseph also asked about the pattern of laxative use in study patients. Dr. Lefkowitz indicated that bulking agents were allowed as long as the dose was kept constant throughout the study. All other laxatives were prohibited. Novartis is preparing a list of laxative use by study week for patients who used prohibited laxatives.

Biostatistics: Dr. Castillo requested that we provide a scientific rationale for the reclassification of the co-primary variable, SGA of abdominal discomfort/pain, to a secondary variable. Dr. Lefkowitz reviewed the evolution of how we came to choose the primary variables, and how the VAS fell out of favor within the medical community, hence we retained it only as a secondary variable. She also questioned why we did not revise the sample size after the endpoint revision, and Dr. Lefkowitz explained that the studies were already clinically complete at the time.

Dr. Castillo noted that the dates for _____ which we provided for the three phase 3 studies (April 19 submission) do not coincide with the dates provided in the database. Dr. Shi will investigate this and provide a response.

Dr. Castillo also wanted to know why a protocol amendment was not prepared for the increase in the number of study sites for B301 and B307, as well as the addition of South African and US study sites to B301. Dr. Lefkowitz noted that this was merely an oversight.

The remaining time during the meeting was devoted to discussion of the Division's comments to the draft briefing documentation which was submitted April 20, 2000. (See attached) The most substantive discussions are noted below:

WITHHOLD 16 PAGE (S)

Memorandum of Meeting Minutes

Meeting Date: May 8, 2000
Meeting Time: 3:30 pm – 5:00 pm
Meeting Place: Potomac Conference Room, Parklawn Building

Application Number: NDA 21-200, Zelmac™ (tegaserod) Tablets

Type of Meeting: 90-Day Conference, Type C
Meeting Chair: Dr. Lilia Talarico
Meeting Recorder: Mr. Paul E. Levine, Jr.

FDA Attendees:

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Lilia Talarico, M.D.; Division Director
Steven Aurecchia, M.D.; Deputy Division Director
Hugo Gallo-Torres, M.D.; Medical Team Leader, Gastrointestinal Drugs
Raymond Joseph, M.D.; Medical Reviewer
Jasti Choudary, Ph.D.; Pharmacology Team Leader
Ke Zhang, Ph.D.; Pharmacology Reviewer
Liang Zhou, Ph.D.; Chemistry Team Leader
Julie Dubeau, Regulatory Health Project Manager
Paul E. Levine, Jr., R.Ph.; Regulatory Project manager

Office of Drug Evaluation III (HFD-103)

Florence Houn, M.D., M.P.H., F.A.C.P., Office Director

Division of Pharmaceutical Evaluation (HFD-870)

Suresh Doddapaneni, Ph.D., Biopharmaceutics Team Leader/Reviewer

Division of Biometrics II (HFD-715)

Tom Permutt, Ph.D., Statistical Team Leader
Sonia Castillo, Ph.D., Statistical Reviewer

External Constituent Attendees:

Novartis Pharmaceuticals Corporation

Thomas Koestler, Ph.D., Global Head of Regulatory Affairs
Mr. Adrian Birch, Global Head DRA, CME TA

Lawrence Hauptman, Ph.D., Director, DRA
Ms. Donna Vivello, Associate Director, CME TA
Martin Lefkowitz, M.D., Director, Clinical Research & Development
Peter Rueegg, Sr., M.D., Clinical Research Physician, Clinical Research and Development
James Mcleod, M.D., Ph.D., Executive Director, Clinical Pharmacology
Yann Tong Chiang, Ph.D., Associate Director, Biostatistics
Phillip Bently, Ph.D., US Head Preclinical Safety

[]

Ms. Lisa Pitt, Assistant Director, DRA
Ms. Cathy Ford, Associate Director DRA-CMC
Yungai Shai, Ph.D., Statistician
Russ Hume, Regulatory Liaison

Background:

On February 11, 2000, the firm submitted NDA 21-200 for Zelmac™ (tegaserod) Tablets with the following proposed indication: the treatment of _____ patients with Irritable Bowel Syndrome (IBS) who identify _____ constipation as their predominant symptoms. The NDA is designated as a priority application with a User Fee Goal Date of August 11, 2000, and is scheduled for a Gastrointestinal Advisory Committee (GIAC) meeting on June 26, 2000.

On March 13, 2000, the firm submitted a request for a 90-Day Conference, in accordance with 21 CFR 314.102, to discuss the general status and any outstanding deficiencies concerning review of the application.

The firm also proposed to discuss plans for the presentation and background package for the upcoming GIAC meeting for Zelmac™. On April 20, 2000, the firm submitted a draft Advisory Committee background package for review. It was agreed that the majority of the meeting would focus on discussions of the proposed background package.

Status of Reviews

The primary reviews for this application are pending. Please provide the following information:

Statistical:

1. Results for both the initial and revised definitions of endpoint responders for each Phase 3 study.
2. Treatment differences in addition to the p-values for each study analysis.

Pharmacology/Toxicology:

Separation of the incidences of ovarian cysts in the rat carcinogenicity study into luteal and follicular types.

Clinical:

1. Data related to the effect of menses on patients taking Zelmac.
2. Information on study patients with Pelvic Inflammatory Disease (PID) or endometriosis.
3. Detailed information on the gender effect on pK.
4. Data on the incidence of study patients with either cholecystectomy or dysmenorrhea. Include all clinical information obtained for these patients.
5. The incidence of constipation-predominant, IBS patients in the United States compared to foreign countries.

Discussion Topics:

The Division's comments (bolded) regarding the draft Advisory Committee background package and the firm's response are as follows:

┌

└

WITHHOLD 8 PAGE (S)

Conclusions:

- [
-]
- [
-]
4. The firm will provide the results for both the initial and revised definitions of endpoint responders for each Phase 3 study.
 5. The firm will provide treatment differences in addition to the p-values for each study analysis.
 6. The firm will separate the incidences of ovarian cysts in the rat carcinogenicity study into luteal and follicular types.
 7. The firm will provide data related to the effect of menses on patients taking Zelmac.

8. The firm will provide information on study patients with Pelvic Inflammatory Disease (PID) or endometriosis.
9. The firm will provide detailed information on the gender effect on pK.
10. The firm will provide data on the incidence of study patients with either cholecystectomy or dysmenorrhea.
11. The firm will provide include all clinical information obtained for these patients.
12. The firm will provide the incidence of constipation-predominant, IBS patients in the United States compared to foreign countries.

Signature, Minutes Preparer: _____

/S/

Concurrence Chair (or designated signatory): _____

/S/

9-11-00

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF MEETING MINUTES

Meeting Date: March 7, 2000
Time: 2:00-3:30 PM
Location: Conference Room 6B-45, Parklawn Building

Application: NDA 21-200
Zelmac (tegaserod) Tablets

Type of Meeting: 45-Day Filing Meeting

Meeting Chair: Dr. Lilia Talarico

Meeting Recorder: Paul E. Levine, Jr.

FDA Attendees:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Lilia Talarico, MD, Division Director
Steve Aurecchia, MD, Division Deputy Director
Hugo Gallo-Torres, MD, Medical Team Leader, Gastrointestinal Drug Products
Raymond Joseph, MD, Medical Reviewer
Jasti Choudary, Ph.D., Pharmacology Team Leader
Ke Zhang, Ph.D., Pharmacology Reviewer
Liang Zhou, Ph.D., Chemistry Team Leader
Ray Frankewich, Ph.D., Chemistry Reviewer
Suresh Doddapaneni, Ph.D., Biopharmaceutics Team Leader
Julie DuBeau, Regulatory Health Project Manager
Paul E. Levine, Jr., R.Ph, Regulatory Project Manager

Division of Biometrics II (HFD-715)

Paul Flyer, Ph.D., Statistician Team Leader
Sonia Castillo, Ph.D., Statistical Reviewer

Division of Scientific Investigations (HFD-45)

Khairy Malek, M.D.

Background:

Novartis Pharmaceuticals Corporation, submitted NDA 21-200 on February 11, 2000, (received February 11, 2000) for Zelmac™ (tegaserod) Tablets with the following proposed indication: for the treatment of _____ patients with irritable bowel syndrome (IBS) who identify _____ constipation as their predominant symptoms.

Meeting Objective:

To determine the fileability of this application, and to discuss any information requests that need to be issued to the sponsor.

Discussion Points:

I. Administrative

A. Filing Issues: None

B. Information Requests/Discussion:

1. The firm will be asked to provide a statement that all manufacturing facilities are ready for inspection.
2. The firm will be asked to provide the unannotated package insert on diskette.
3. The paper copy of the annotated package insert was not discovered initially but was later found in the summary volume. Vol. 1, p. 3:2-18
4. The firm will be asked to provide a layout (visual) of the immediate container and carton labels. Only the words to be included on the immediate container and carton labels were submitted.
5. The firm will be asked to provide a statement certifying that all information contained on CDROM are identical to the information contained in the paper submission. Each reviewer received a CDROM which are intended to be reviewer aid copies of information submitted in paper and electronically to the NDA. A cursory review of the CDROM by the project manager indicated that the information appeared to be identical to that submitted in paper. Certification of this fact from the firm is required.
6. The firm will be asked to provide stability data on diskette. Dr. Choudary stated that he did not need animal tumorigenicity data on diskette.

II. Clinical

A. Filing Issues: None

B. Information Requests/Discussion:

1. The drug is a new molecular entity, intended for use in a population ~~male~~ female constipation predominant IBS patients) where no current therapy exists. A Priority designation with office level signature is indicated.
2. The firm was only able to demonstrate efficacy in one study and was able to demonstrate efficacy in another after modifying the endpoints. In a third study, efficacy was not demonstrated. In addition, there may be safety issues to be addressed once the application is fully reviewed. Comments from the Gastrointestinal Advisory Committee (GIAC) members may be useful in addressing these issues.
3. Clinical sites to be inspected will be determined after further review of the application. The medical officer will submit inspection sites directly to DSI.

III. Pharm/Tox

A. Filing Issues: None

B. Information Requests/Discussion:

1. Dr. Choudary stated that the carcinogenicity information was submitted under IND
— The firm should submit a statement verifying that carcinogenicity data in the NDA is identical to that submitted to the IND.
2. Carcinogenicity data will need to be presented to Carcinogenicity Assessment Committee (CAC).

IV. Chemistry\Manufacturing\Controls (CMC)

- A. Filing Issues: None
- B. Information Requests/Discussion: None

V. Biopharmaceutics

- A. Filing Issues: None
- B. Information Requests/Discussion: None

VI. Statistical

- A. Filing Issues: None
- B. Information Requests/Discussion:
 1. Provide a copy of the pre-NDA meeting minutes and background information submitted to the IND.
 2. Firm will be requested to provide an electronic copy of safety information, or provide current location if already submitted to NDA

Conclusions:

1. It was determined that the application would be filed.
2. Because this compound potentially offers a meaningful therapeutic benefit over available therapy, the application has been designated as "Priority". Therefore, the FDAMA Goal Date is August 11, 2000.
3. Since this application is a new molecular entity (NME), any action will require office level signature.
4. The Project Manager will submit a request to the Advisory and Consultant Staff (ACS) Executive Secretary for a GIAC Meeting to be held in June. The ACS will be asked to comment on efficacy and possible safety issues concerning this application.
5. The Project Manager will communicate to the firm in a telephone conference the information requests resulting from the administrative review and the Statistical review as indicated above (I.B.1, 2, 4, 5, 6; III.B.2; and VI.B.2). In addition, the firm will be notified that the application will be submitted to the GIAC.
6. It was agreed that the next team meeting would be held during the first week of April. A "Zelmac™ - Review Plan", which includes meetings and internal goal dates, will be finalized and distributed at that meeting.

Minutes Preparer

Chair Concurrence

/S/

/S/

3/21/00

3-21-00

“BIMO REVIEW COPY”

Presubmission (two copies)

1. NDA number, name and telephone number of sponsor's contact person. [314.50(a)]
2. A summary of the clinical data section of the application, including the results of statistical analyses of the clinical trials. [314.50(c)(2)(viii) or 314.50(d)(5)(ii)]
3. Identification of all important/pivotal studies, foreign and domestic for each indication, listed by titles with protocol number and amendments and dates of amendments. [314.50(d)(5)(ii)]
4. Copy of each protocol for important/pivotal studies. [314.50(d)(5)(ii) and/or (iii)]
5. Names and addresses of principal investigators who conducted these important/pivotal studies. [314.50(d)(5)(ii)]
6. Number of subjects enrolled in each study arm at each site and the number of subjects dropped-out at each site. [314.50(d)(5)(ii) or (f)]
7. List and identification of treatment-limiting adverse events including deaths reported per site. [314.50(f)]
8. The sponsor-monitor for each study. [314.50(d)(5)(ii)]
9. If a sponsor has transferred any obligations for the conduct of any clinical study to a Contract Research Organization, a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred. If all obligations governing the conduct of the study have been transferred, a general statement of this transfer-in lieu of a listing of the specific obligations transferred-may be submitted. [314.50(d)(5)(x)]
10. If original subject records were audited or reviewed by the sponsor in the course of monitoring any clinical study to verify the accuracy of the case reports submitted to the sponsor, a list identifying each clinical study so audited and reviewed. [314.50(d)(5)(xi)]

Additional information which may be requested as per BIMO reviewer:

1. Selected completed case report forms (CRFs). [314.50(f)]
2. Specified data tabulations. [314.50(f)]
3. Coding key/randomization list.
4. List of primary efficacy end point data. [314.50(d)(5)(ii) and (f)]
5. Number of evaluable and non-evaluable subjects. [314.50(d)(5)(ii)]
6. List of discontinued subjects and the reason(s). [314.50(d)(5)(ii)]
7. Adverse events, other than serious with descriptions. [314.50(d)(5)(ii) or (f)]

Please send two (2) copies of the "BIMO Review Copy" to:

**Food and Drug Administration
Division of Scientific Investigation (HFD-344)
Attention: Dr. Khairy Malek
7520 Standish Place
Rockville, MD 20855**

and a copy of the cover letter (not the whole "BIMO Review Copy" submission) to the review division at:

**Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Office Of Drug Evaluation and Research III
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857**

If you have any questions concerning this submission, please contact Dr. Malek at 301-594-1032.

**APPEARS THIS WAY
ON ORIGINAL**

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE

CENTER FOR DRUG EVALUATION AND RESEARCH

Chair

Hanauer, Stephen M.D. 6/30/00
 Professor Medicine & Clinical Pharmacology
 The University of Chicago
 Department of Medicine
 5841 South Maryland Ave.
 Chicago, Illinois 60637

EXECUTIVE SECRETARY

Tom Perez, M.P.H.
 Health Science administrator
 Food and Drug Administration
 5600 Fishers Lane - HFD-21
 Building 5630
 Rockville, MD 20857

Members

MEMBERS

CONSUMER REPRESENTATIVE

Rosemary Berardi, Pharm.D. 6/30/00
 Professor of Pharmacy
 College of Pharmacy
 The University of Michigan
 128 Church Street
 Ann Arbor, Michigan 48109

Roberto Groszmann, M.D. 6/30/00
 Professor of Medicine
 Department of Veteran Affairs
 University School of Medicine
 Conn. Healthcare System, Bldg 11/J
 150 Campbell Avenue
 West Haven, Connecticut 06516

Looren Laine, M.D. 6/30/00
 JSC School of Medicine
 Gastrointestinal & Liver Disease Division
 JAC 12-137, Department of Medicine
 University of South California School of Medicine
 1025 Zonal Avenue
 Los Angeles, CA 900331

George D. Ferry, M.D. 6/30/01
 Professor of Pediatrics
 Texas Children's Hospital
 Gastroenterology and Nutrition
 621 Fannin Street (MD 3-3391)
 Houston, Texas 77030

Villiam M. Steinberg, M.D. 6/30/01
 106 Irving Street, N.W.
 Suite 205, South Tower
 Washington, DC 20010
 Dr 5530 Wisconsin Ave.
 Chevy Chase, MD 20815

Christina M. Surawicz, M.D. 6/30/01
 Professor of Medicine
 Harborview Medical Center
 325 9th Avenue, Box 359773
 Seattle, Washington 98104

Nancy L., Geller, Ph.D. 6/30/02
 Chief, Biostatistics Research Branch
 National Heart, Lung, and Blood Institute
 National Institutes of Health
 Rockledge Centre 2, Room 8210
 6701 Rockledge Drive, MSC 7938
 Bethesda, Maryland 20892

Joanne A.P. Wison, M.D. 6/30/02
 Professor of Medicine
 Duke University Medical Center
 Erwin Road, Bell Building, Room 222
 Durham, North Carolina 27701

Joel Richter, M.D. 06/30/03
 Professor of Internal Medicine
 Department of Gastroenterology/S40
 The Cleveland Clinic Foundation
 9500 Euclid Ave. Building 540
 Cleveland, Ohio 44195

M. Michael Wolfe, M.D. 06/30/03
 Professor of Medicine and Physiology
 Boston University School of Medicine
 650 Albany Street
 Boston, MA 02118

Questions for the Gastrointestinal Drugs Advisory Committee
June 26, 2000

Novartis Pharmaceuticals Corporation has requested approval for Zelmac™ (tegaserod) Tablets for the treatment of irritable bowel syndrome (IBS) in patients who identify abdominal pain/discomfort and constipation as their predominant symptoms. The sponsor recommends a dose of 6 mg po BID within 30 minutes prior to a meal.

1. Has efficacy been demonstrated in both men and women with constipation-predominant IBS?
 - (a) If not, in which gender was efficacy demonstrated?
 - (b) If yes (for both genders or one), which of the following dose(s) demonstrated efficacy?
 - (i) 4 mg/day
 - (ii) 12 mg/day
 - (iii) titrated dose regimen from 4 mg/day to 12 mg/day
2. Please comment on the following findings of the carcinogenicity studies.
 - (a) Mucosal hyperplasia and adenocarcinoma of the small intestine were observed in (CD-1) mice at the tegaserod dose of 600 mg/kg/day but not at 200 or 60 mg/kg/day.
 - (b) An apparent increased incidence of ovarian follicular cysts at 110 weeks of age was observed in (Han/Im Wistar) rats.
3. In the clinical trials, diarrhea was seen in greater proportion in patients receiving Zelmac™. Please comment on this finding.
4. In the clinical trials, lower abdominal pain leading to laparotomy occurred in greater proportion in patients receiving Zelmac™. Please comment on this finding.
5. On the basis of your benefit-risk evaluation, do you recommend that Zelmac™ be approved for the indication requested by the sponsor?
 - (a) If yes,
 - (i) what labeling recommendations do you have to reduce the potential risks of Zelmac™?
 - (ii) what recommendations do you have for post-marketing studies or risk management programs to address any remaining concerns?
 - (b) If not, what additional efficacy and/or safety data should the sponsor provide?